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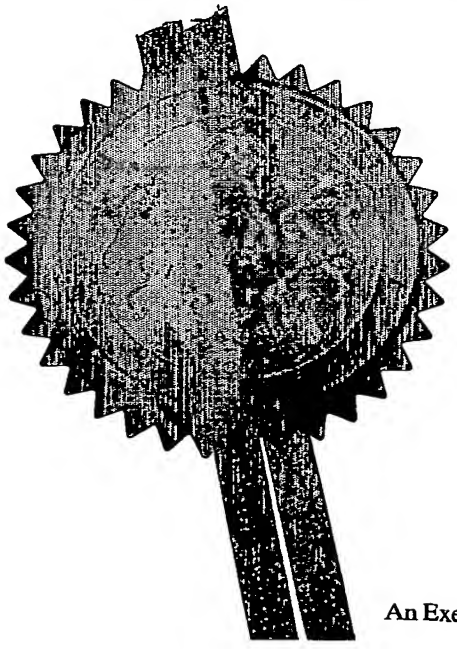

Signed R. Mahoney

Dated 17 April 2003

Patents Form 1/77

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15 OCT 2002

The **Patent Office**

1/77

160702 E753869-7 D00524
P01/7700 0.00-0223977.0

Request for grant of a patent

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1.	Your reference	G-32503P1/ABR 9922
2.	Patent application number *(The Patent Office will fill in this part)*	0223977.0 15 OCT 2002
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	BIOCHEMIE GBESELLSCHAFT MBH A-6250 KUNDL TIROL AUSTRIA
	Patent ADP number *(if you know it)*	8355158001
	If the applicant is a corporate body, give the country/state of its incorporation	AUSTRIA
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*	Yes
	a) any applicant named in part 3 is not an inventor, or	
	b) there is an inventor who is not named as an applicant, or	
	c) any named applicant is a corporate body.	
	(see note (d))	

Patents Form 1/77

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Continuation sheets of this form	
Description	8
Claim(s)	2
Abstract	1
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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	One
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B.A. Yorke & Co Date **15 October 2002**

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

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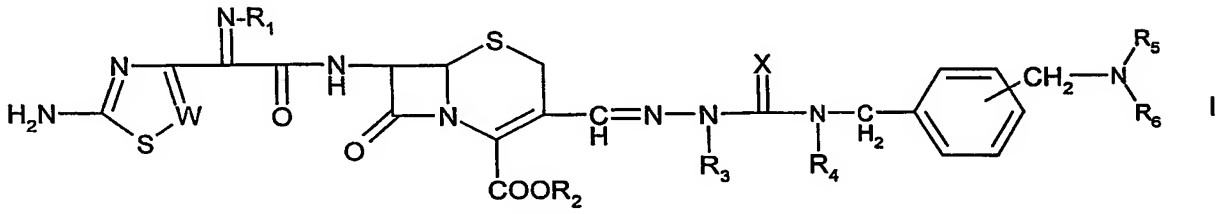
Organic compounds

The present invention relates to organic compounds e.g. antimicrobial compounds such as cephalosporins.

In one aspect the present invention provides a compound of formula



I

wherein

W is CH or N,

R_1 is hydrogen or O-R_1`

R_1` is hydrogen, (C_{1-6})alkyl, halo(C_{1-6})alkyl or hydroxycarbonyl(C_{1-6})alkyl,

R_2 is hydrogen or an ester moiety,

R_3 is hydrogen, (C_{1-2})alkyl, allyl or (C_{3-8})cycloalkyl,

R_4 is hydrogen or (C_{1-2})alkyl,

R_5 and R_6 independently of each other are hydrogen, (C_{1-6})alkyl, (C_{1-6})alkyl-carbonyloxy, arylcarbonyloxy, (C_{1-6})alkylsulfonyl or arylsulfonyl, and

X = NH, O or S.

$CH_2NR_5R_6$ can be in o, m or p position.

In a preferred aspect the present invention provides a compound of formula I wherein R_1 is hydroxy or fluoromethoxy, R_2, R_4, R_5 and R_6 are hydrogen, R_3 is methyl and the group $CH_2NR_5R_6$ group is in p position.

An ester moiety includes alkyl; e.g. unsubstituted alkyl or substituted alkyl, e.g. by aryl, such as benzyl, alkoxybenzyl, such as 4-methoxybenzyl, alkoxy, such as methoxymethyl; alkyloxycarbonyloxy; alkyl; alkoxy, such as glycyloxy, phenylglycyloxy, e.g. glycyloxymethyl, phenylglycyloxymethyl; heterocyclyl e.g. 5-methyl-2-oxo-1,3-dioxolen-4-yl; indanyl, phthalidyl, alkoxycarbonyloxy and ester moieties which form with the COO^- group a physiologically hydrolysable and acceptable ester, *e.g.* such known to be hydrolysable ester groups in the field of cephalosporins. A compound of formula I may thus be in the form of an

physiologically-hydrolysable and -acceptable ester. By physiologically-hydrolysable and -acceptable esters as used herein is meant an ester in which the COO- group is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at dosages to be administered. The term is thus to be understood as defining regular pro-drug forms. An ester moiety may be preferably a group which is easily hydrolysable under physiological conditions. Such esters may be administered preferably orally. Parenteral administration may be indicated if the ester *per se* is an active compound or, if hydrolysis occurs in the blood.

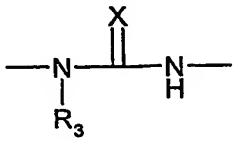
If not otherwise indicated herein any carbon containing group may contain up to 20 carbon atoms. Aryl includes (C_{6-18})aryl, preferably phenyl, naphthyl, e.g. phenyl.

Any group(s) may be unsubstituted or one or morefold substituted, e.g. by groups as conventional in cephalosporin chemistry.

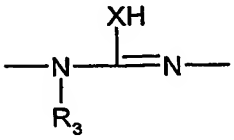
In this specification unless otherwise indicated terms such as "compound of formula I" embrace the compound in any form, for example in the form of a salt and in free base form. The present invention thus includes a compound in free base form or, e.g. where such forms exist, in the form of a salt, for example in the form of an acid addition salt, inner salt, quaternary salt and/or in the form of a solvate, for example in the form of a hydrate. A salt may be a pharmaceutically acceptable salt of a compound of formula I such as a metal salt or an amine salt. Metal salts include for example sodium, potassium, calcium, barium, zinc, aluminum salts, preferably sodium or potassium salts. Amine salts include for example trialkylamine, procaine, dibenzylamine and benzylamine salts. The amino group of the cyclohexyl ring in a compound of formula I may be e.g. a NH_3^+ group, $NR_5R_6R_7^+$, NHR_5R_6 or NH_2R_5, wherein R_5 and R_6 have the before said meanings and R_7 independently of R_5 and R_6 may have the same meaning as those. Counterions are those as conventional, e.g. hydroxy or chloride ions. A free form of a compound of formula I may be converted into a salt form, a solvate form or a salt and a solvate form and *vice versa*.

In a further aspect the present invention provides a compound of formula I in the form of a salt, for example an acid addition salt or a metal salt, e.g. and a compound of formula I in free form, in the form of a salt, in the form of a solvate or in the form of a salt and a solvate.

The present invention includes a compound of formula I in any isomeric/tautomeric from in which it may exist. E.g. the configuration in group



may (co)exist in the form of

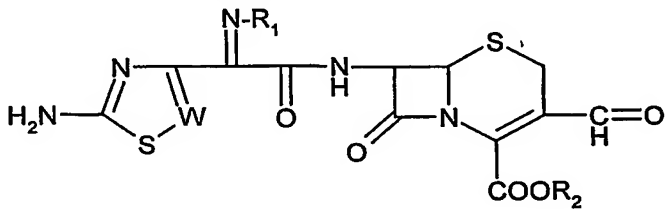


Also e.g. geometric isomers if R_1 is other than hydrogen may be syn [(Z)] and anti [(E)] and is preferably syn [(Z)]. E.g. a chiral carbon atom may be introduced, e.g. during a production process of a compound of formula I and corresponding stereoisomeric forms of a compound of formula I may be obtained, e.g a mixture of the individual stereoisomers, e.g. a racemate, or pure isostereoisomeric forms. Mixtures of isomers may be separated according to a method of conventional.

The present invention includes a compound of formula I in any tautomeric form, in any isomeric mixtures and in the form of pure isomers.

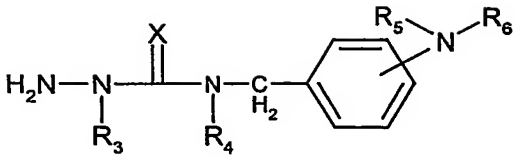
Any compound mentioned herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. analogously to a method as conventional or as disclosed herein.

In another aspect the present invention provides a process for the production of a compound of formula I by reacting a compound of formula



(II)

wherein R_1 and R_2 are defined as described before, with a compound of formula



(III)

wherein R_3, R_4, R_5 and R_6 are defined as described before.

If desired, reactive groups may be protected with protecting groups, which may be, or, which are split off under the reaction conditions, or after the reaction. A compound of formula I wherein R_2 is hydrogen may be converted into a compound of formula I wherein R_2 is an carboxylic acid ester group. A compound of formula I may be isolated from the reaction mixture as appropriate, e.g. analogously to a method as conventional.

The compounds of formula I including salt/solvate, hereinafter designated as "active compound(s) of the invention" exhibit pharmacological activity, e.g. beside low toxicity and are therefore useful as pharmaceuticals. In particular, the active compounds of the invention show antimicrobial, *e.g.* antibacterial, activity against e.g. gram negative and gram positive bacteria, e.g. gram positive bacteria, such as *e.g.* Escherichia, e.g. Escherichia coli; Enterobacter, e.g. Enterobacter cloacae; Enterococcus, e.g. Enterococcus faecalis; Klebsiella, e.g. Klebsiella pneumoniae; Streptococcus, e.g. Streptococcus pneuminiae; Staphylococcus, e.g. Staphylococcus aureus; and Pseudomonas, e.g. Pseudomonas aeruginosa, in vitro in the Agar Dilution Test according to National Commitee for Clinical Laboratory Standards (NCCLS) 1993, Document M7-A3Vol.13, No. 25: "Methods for dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition, Approved Standard". The active compounds show an MIC (µg/ml) in the Agar Dilution Test from about <0.0125 to ca. >6.25. The active compounds of the invention show a surprising overall activity spectrum. The activities for a salt form and/or a solvate form of the compound of formula I are in the same range as the activity of the compound of formula I in free form.

In another aspect the present invention provides an active compound for use as a pharmaceutical, preferably as an antimicrobial agent, such as an antibiotic.
In a further aspect the present invention provides an active compound of the present invention for use in the preparation of a medicament for the treatment of microbial diseases, for example diseases mediated by bacterias selected from *Escherichia, Enterobacter, Enterococcus, Klebsiella, Streptococcus, Staphylococcus and Pseudomonas.*
The present invention provides in further aspects

- an active compound of the present invention for use as a pharmaceutical in the treatment of microbial diseases caused by bacterias selected from Escherichia, Enterobacter, Enterococus, Klebsiella, Streptococcus, Staphylococcus and Pseudomonas; and
- the use of an active compound of the present invention or the use of a pharmaceutical composition comprising an active compound of the present invention as a pharmaceutical

In a further aspect the present invention provides a method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of an active compound of the present invention.
Treatment includes disease treatment as well as prophylactic treatment.

For this indication, the appropriate dosage will, of course, vary depending upon, for example, the compound of formula I used, the host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from about 0.05 to 5 g, for example 0.1 to about 2.5 g, of an active compound of the invention conveniently administered, for example, in divided doses up to four times a day.
An active compound of the invention may be administered by any conventional route, for example orally, *e.g.* in form of tablets or capsules, or parenterally in the form of injectable solutions or suspensions, e.g. in analogous manner to ceftazidime.

The compound of example 1 is a preferred compound of the present invention.
It has, for example been determined that the MIC (µg/ml) of the compound of Example 1 against, for example Klebsiella pneumoniae is about 0.0125. It is therefore, indicated that for the treatment of microbial diseases, *e.g.* bacterial diseases, the preferred compounds of the invention may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally used with ceftazidime.

The compounds of formula I may be administered in pharmaceutically acceptable salt form, *e.g.* acid addition salt form or base addition salt form or in the corresponding free forms, optionally in solvate form. Such salts exhibit the same order of activity as the free forms.

In another aspect the present invention provides a pharmaceutical composition comprising an active compound of the present invention in association with at least one

pharmaceutically excipient. Such compositions may be manufactured accordingly, e.g. analogously to a method as conventional. Pharmaceutical excipient(s) include(s) pharmaceutically active excipient.

In the following examples which illustrate the present invention all temperatures are given in degree centigrade. RT means room temperature.

EXAMPLE 1

A) SYNTHESIS OF INTERMEDIATE COMPOUNDS

a) Benzylidene derivative of 3-amino-1-[3-(aminomethyl)benzylamino]-3-methyl-guanidine in the form of a monohydrochloride

35 g of the benzylidene derivative of S-methyl-2-methyl-isothiosemicarbazide in the form of a hydrochloride and 32.79 g of 3-aminomethylbenzol in 300 ml of MeOH are refluxed. The mixture obtained is stirred at RT, a precipitate forms, is filtered off and solvent is evaporated. The evaporation residue obtained is treated with 217.5 ml of 2M HCl, a precipitate formed is filtered off, washed and dried. The volume of the filtrate obtained is brought to about 150 ml, a precipitate is formed, filtered off, washed and dried. The dried, combined precipitates are recristallized from water and the benzylidene derivative of 3-amino-1-[3-(aminomethyl)-benzylamino]-3-methyl-guanidine in the form of a monohydrochloride is obtained.

b) 3-amino-1-[3-(aminomethyl)benzylamino]-3-methyl-guanidine dihydrochloride

From a mixture of 24.74 g of the benzylidene derivative of 3-amino-1-[3-(aminomethyl) benzylamino]-3-methyl-guanidine in the form of a monohydrochloride in 79.9 ml of 2M HCl, benzaldehyde is destilled off and solvent from the remaining mixture is evaporated. 3-amino-1-[3-(aminomethyl)-benzylamino]-3-methyl-guanidine is obtained in the form of a dihydrochloride.

B) SYNTHESIS OF SUBSTITUTED CEPHALOSPORINES

a) 3-{(E)[[1-[3-(aminomethyl)benzylamino]-iminomethyl]-methylhydrazono] methyl}-7-{[(5-amino-[1,2,4]thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino}-3-cephem-4-carboxylic acid trihydrochloride

To a mixture of 2 g of 3-[amino-1-(aminomethyl)benzylamino]-3-methyl-guanidine in the form of a dihydrochloride in 3.4 ml of 2M HCl and 6.1 ml dimethylacetamide, 2.78 g of N-(1,4,5a,6-tetrahydro-3-hydroxy-1,7-dioxo-3H,7H-azeto(2,1-b)furo(3,4-d)(1,3)-thiazin-6-yl)-2-(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-2-(fluoromethoxyimino) acetic acid amide are added and the suspension obtained is stirred at RT. The mixture obtained is poured into acetonitrile under stirring. A precipitate formed is filtrated off, washed and dried. 3-{(E)[[1-[3-(aminomethyl)benzylamino]-iminomethyl]-methylhydrazono] methyl}-7-{[(5-amino-[1,2,4]thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino}-3-cephem-4-carboxylic acid is obtained in the form of a trihydrochloride.

b) 3-{(E)[[1-[3-(aminomethyl)benzylamino]-iminomethyl]-methylhydrazono] methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]

amino}-3-cephem-4-carboxylic acid monohydrochloride

10 g of the crude 3-{(E)[[1-[3-(aminomethyl)benzylamino]-iminomethyl]-methylhydrazono] methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl] amino}-3-cephem-4-carboxylic acid in the form of a trihydrochloride are dissolved in 42 ml of water and subjected to chromatography (e.g. LiChroprep RP-18^R, Merck, grain size 40-63 um). Fractions containing the desired compound in the form of a monohydrochloride (HPLC determination) are combined and optionally lyophilised. 3-{(E)[[1-[3-(aminomethyl)benzyl-amino]-iminomethyl]-methyl-hydrazono]methyl}-7-{[(5-amino-1,2,4-thiadiazol-3-yl)-(Z)-(fluoromethoxyimino)-acetyl]amino}-3-cephem-4-carboxylic acid is obtained in the form of a monohydrochloride, optionally as a lyophilizate.

^{1}H-NMR (200 MHz, DMSO-d_6)

3.41, s, 3H, NCH_3; 3.52, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 3.88 – 4.12, m, 2H, NCH_2; 4.40 – 4.80, m, 3H, 2H from NCH_2 and 1H from SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.96, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 7.22 – 7.58, m, 4H, aromatic H; 8.14, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH

According to the method as described in Example 1, but using the appropriate starting materials the following compounds are obtained.

Example 2: Compound of formula I wherein R_1 is OCH_2F, R_3 is CH_3, R_2, R_4, R_5, R_6 are H and the $CH_2NR_5R_6$ group is in p position:

^{1}H-NMR (200 MHz, DMSO-d_6)

3.38, s, 3H, NCH_3; 3.52, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 3.90 – 4.12, m, 2H, NCH_2; 4.50 – 4.80, m, 3H, 2H from NCH_2 and 1H from SCH_2; 5.28, d, J=5 Hz, 1H, ß-lactam; 5.78, d, J=55 Hz, 2H, CH_2F; 5.96, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 7.28 – 7.60, m, 4H, aromatic H; 8.14, s, 1H, CH=N; 9.84, d, J=8 Hz, 1H, NH.

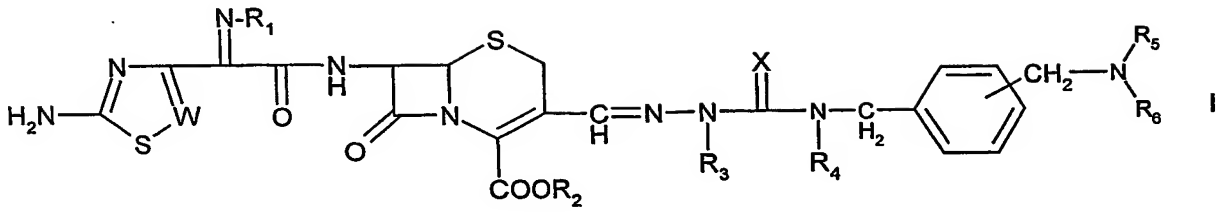
Example 3: Compound of formula I wherein R_1 is OH, R_3 is CH_3, R_2, R_4, R_5, R_6 are H and the $CH_2NR_5R_6$ is in p position:

^{1}H-NMR (200 MHz, DMSO-d_6)

3.37, s, 3H, NCH_3; 3.57, part of the AB-quartet, J=18 Hz, 1H, SCH_2; 3.90 – 4.10, m, 2H, NCH_2; 4.45 – 4.75, m, 3H, 2H from NCH_2 and 1H from SCH_2; 5.15, d, J=5 Hz, 1H, ß-lactam; 5.74, dd, J=5 Hz and 8 Hz, 1H, ß-lactam; 6.88, s, 1H, CH thiazol; 7.20 – 7.55, m, 4H, aromatic H; 8.15, s, 1H, CH=N; 9.78, d, J=8 Hz, 1H, NH.

Patent claims

1. A compound of formula



I

wherein

W is CH or N,

R_1 is hydrogen or O-R_1`

R_1` is hydrogen, (C_{1-6})alkyl, halo(C_{1-6})alkyl or hydroxycarbonyl(C_{1-6})alkyl,

R_2 is hydrogen or an ester moiety,

R_3 is hydrogen, (C_{1-2})alkyl, allyl or (C_{3-8})cycloalkyl,

R_4 is hydrogen or (C_{1-2})alkyl,

R_5 and R_6 independently of each other are hydrogen, (C_{1-6})alkyl, (C_{1-6})alkyl-carbonyloxy, arylcarbonyloxy, (C_{1-6})alkylsulfonyl or arylsulfonyl, and

X = NH, O or S.

2. A compound of formula I wherein R_1 is hydroxy or fluoromethoxy, R_2, R_4, R_5 and R_6 are hydrogen, R_3 is methyl and the group $CH_2NR_5R_6$ group is in p position.

3. A compound according to claim 1 or 2 in the form of a salt.

4. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3 in association with at least one pharmaceutical excipient.

5. A compound according to any one of claims 1 to 3 for use as a pharmaceutical.

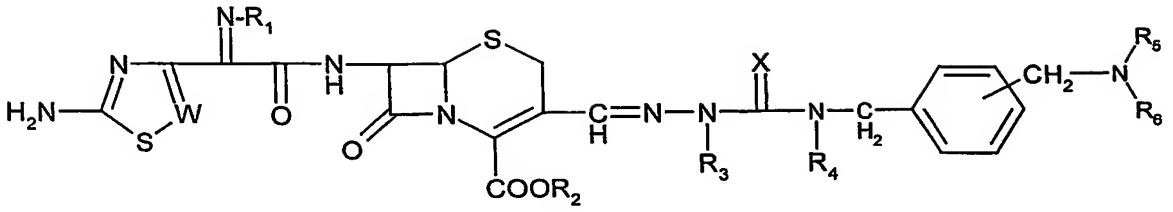
6. A compound according to claim 5 for the treatment of microbial diseases.

7. A method of treatment of microbial diseases which comprises administering to a subject in need of such treatment an effective amount of a compound according to any one of claims 1 and 4.

IL/14-Oct-2002

Abstract

A compound of formula



I

wherein the substituents have various meanings, useful as a pharmaceutical.

IL/14-Oct-2002